removal of three laminæ in the dorsolumbar region. According to these authors, however, it is difficult to recognize the roots to be cut, and there is danger of division of the anterior roots with the posterior ones.

Based upon the anatomical facts above described, I have, in the cadaver, exposed the lumbosacral cord by the removal of the laminæ of the eleventh and twelfth dorsal or eleventh and twelfth dorsal and first lumbar vertebræ, and have been able to recognize and divide the lumbar and sacral posterior roots desired. I desire to recommend the following method for the exposure and division of posterior roots to the lower extremities: Removal of the spinous processes and laminæ of the eleventh and twelfth dorsal vertebræ (and of the first lumbar if necessary) in the usual manner; exposure of the "fork" of the dentate ligament and identification of the first lumbar posterior root; careful elevation of all of the posterior roots of the side to be operated upon (which lie dorsal to the lateral fibrous band on the side of the lumbosacral cord) upon a bent probe passed under them; identification and isolation of the desired posterior roots by counting from the first lumbar root; division of the roots in the usual manner.

BENCE-JONES PROTEINURIA: A REPORT OF FOUR CASES, WITH SOME CHEMICAL AND BIOLOGICAL NOTES.[1]

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I. Introduction. Having had the unusual opportunity of studying, with more or less completeness, 4 cases of Bence-Jones proteinuria, it seems to the writers worth while to record these briefly with some observations on the methods of recognition, chemical properties of the body, and certain biological reactions. The work of Magnus-Levy,[2] Grutterink and de Graaf,[3] Abderhalden and Rostoski,[4] and especially the recent exhaustive contribution of Hopkins and Savory,[5] have made it certain that this body is not an albumose, but a true protein, yielding the characteristic amino-acids on hydrolysis. The theories as to its origin are quite numerous, but in the light of recent investigations the more important are those which seek its derivation (1) from the proteins of the tissues or blood, (2) specifically from the tissues of the bones, or (3) as a product of abnormal protein metabolism, either endogenous or exogenous. Of these the preponderance of evidence seems to favor the idea that the enormous output of the protein is rather due to the influence of the tumor, or its products, on the tissue metabolism, than the direct product of a relatively small amount of tumor substance present in the body. The great majority of the cases in which this body has been found in the urine have been instances of multiple myeloma, although not all individuals suffering from this disease have exhibited Bence-Jones proteinuria. In isolated instances it has been found associated with other pathological conditions, such as leukemia, chloroma, lymphosarcoma, myxedema, and carcinomatous metastases (1 case). It is also to be noted that some of the reported occurrences associated with leukemia and osteomalacia were subsequently found to be cases of multiple myeloma. . The most complete historical review which has come to our notice is that of Rosenbloom.[6]

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[1] Read at the meeting of the Association of American Physicians, May 14, 1912.

[2] Zeit. f. phys. Chem., 1900, xxx, 200.

[3] Ibid., 1902, xxxiv, 393; ibid, 1905, xlvi, 472.

[4] Ibid., 1905, xlvi, 125.

II. Case Reports. Case I.—C. F., white, female, aged fifty-four years. Patient of Prof. Gordon Wilson, Baltimore.

Complaint: Rheumatism. Family History: unimportant. Past History: intermittent fever at twenty. When aged twenty-six years fell and hurt left leg, which two years later broke down and ulcerated. Treated several years in the Johns Hopkins Hospital Dispensary. Normally well until October, 1909, when she began to have pains in left leg, which extended to her back and neck, and developed swellings, considered to be rheumatic, in feet and legs, which gradually involved the larger joints of the arms as well. In the winter of 1909 she began to have gastric disturbance, regurgitation of food, not much nausea, no hematemesis, and great wasting. Was considered to have carcinoma of the stomach. Became bedridden, owing to joint troubles and weakness. In May, 1909, she developed severe pains, worse at night, often lancinating in character, in both arms and legs. Gradual atrophy of muscles and stiffness. Severe diarrhea developed in summer of 1910, with abatement of gastric symptoms. Frequent small mucous stools, but no blood. At times incontinence of feces. In the fall and winter of 1910-11, increasing polyuria, with cystitis. Bence-Jones protein was found in the urine by Dr. Wilson in January 1911; it had not been observed in the last previous examination, October, 1910.

[5] Jour. Physiol., 1911, xlii, 189.

[6] (Exhaustive bibliography to 1911) Biochemical Bulletin, 1911, i, 161.

Patient was first seen by us January 20, 1911, at which time she showed great emaciation and rigidity of the extremities. Pupillary reactions normal. There was a moderate stomatitis, with some salivation (not due to mercury). Tongue very thick, pallid, with marked hypertrophy of the papillæ. Buccal mucous membrane opaque and soft. No abnormality in lungs. Heart slightly enlarged, and showed a well-compensated mitral stenosis and insufficiency. Peripheral arteries sclerotic. Pulse of good volume, regular, 80. Blood pressure: systolic, 110 to 120 mm. Hg. Abdomen scaphoid. No abnormal pulsation or peristalsis. No masses made out on palpation. Pelvic organs apparently normal. Extremities: marked thickening about large joints, with limitation of motion and pain on manipulation. No acute inflammatory changes. Terminal phalanges of fingers and toes somewhat enlarged and clubbed. Left tibia was distinctly enlarged throughout the greater part of the shaft, but not rough or irregular. No enlargement of ribs or bone tenderness there or elsewhere in skeleton made out. Rather marked diffuse keratosis in palms and plantar surfaces of feet. Patient was subject to occasional syncopal attacks, in which she apparently had a weak pulse, without convulsions. Marked cutaneous hyperesthesia on palms and soles of feet. At this time there was polydipsia and polyuria. Blood: rather marked secondary anemia. Normal white blood count and differential. Wassermann: negative.

Urine: Amount, twenty-four hours, 2350 c.c.; pale yellow; cloudy; faintly alkaline; specific gravity, 1014; heavy white sediment of granular debris; epithelial cells; no casts, blood, or pus; no sugar; biuret reaction positive; abundant carbonates; uric acid, 0.54 gram; total nitrogen, 12.68 gram; total chlorides, 2.3 gram. (During the last few months of life it was impossible to secure a twenty-four hour specimen, but total amount of urine was about 500 c.c. per day, giving a total chlorides of 3 grams). Polarization after removal of protein negative; diacetic acid and acetone absent; urobilin present; total protein, 2 grams to liter (Tsuchiya); Heller's nitric acid test gave a heavy white ring at contact line; with heat and acetic acid the protein precipitated between 56° C. and 60° C.; partial resolution on boiling and reprecipitation on cooling; filtrate gave no biuret or Adamkiwicz tests; with dilute nitric acid (25 per cent.) characteristic precipitation in the cold, with nearly complete solution on boiling and reprecipitation on cooling.

The case was observed at intervals until her death, May 6, 1912. The polyuria disappeared, partly owing to increasing stomatitis and difficulty in swallowing. Tongue became so large as to practically fill the mouth, deep red in color, marked superficial maceration. In December, 1911, patient was seen again after four months, when a nodule was noted on the anterior border of the left scapula, hard and apparently continuous with the bone. This gradually increased, reaching the size of a hen's egg before death. In February, 1912, there was tenderness over the third and fourth ribs, left precordium, and axilla, but no nodules were made out. This persisted and increased, ribs becoming eventually definitely nodular, and six days before death they caved in. Coincident with this there developed a pericardial friction rub of great intensity with extreme pain. There was tenderness over most of the thoracic spine, but no nodes were discovered. In April, 1912, nodules were noted over the anterior surface of both elbows about the condyles; there was a brawny induration of the fingers, very like scleroderma, with an extraordinary overgrowth of the horny layers of the skin and a hypertrichosis of the hairs of the face. At this time there was noted a mass extending from the anterior superior spine of the ilium on the left side, half-way to the pubis, which was firm, elastic, and exquisitely sensitive. It caused great pain, referred to the distribution of the anterior crural nerve. A similar, but smaller, mass was felt just behind Poupart's ligament on the right side, near the pubis. These, with the nodules on the other bones, increased with great rapidity during the last four weeks of life, the one on the left ilium reaching the size of a large orange. The inguinal, axillary, and epitrochlear glands became enlarged during this period; they were discrete, firm, and sensitive to the touch. The patient lost all ability to swallow, apparently owing to the enormous swelling of the tongue. Articulation was much impaired. She took no food or water during the last week of life.

X-ray examination, made in February, 1912, with a portable apparatus was unsuccessful, with the exception of the plate of the left tibia, which showed an enlarged, swollen tibia. "There were no absolute areas of bone destruction, but there was a laminated rarefaction, extending throughout the tibia. From the *x*-ray examination it would be impossible to state definitely that this change was myeloma. In fact, the bone change simulates more closely the changes one sees in Paget's disease."

No autopsy was permitted.

During the entire period of observation (fifteen and one-half months) the urine showed constantly a reaction for Bence-Jones protein.

Case II.—C. G., white, male, aged fifty-two years. Patient of Prof. H. G. Beck, of Baltimore, who kindly gave us his notes and a specimen of urine after the death of the patient, January 7, 1912.

Abstract of Dr. Beck's notes: "Patient was first seen September 8, 1911. Had been ailing for some months. Complained of shortness of breath, poor memory, weakness, and loss of weight. Physical examination showed arteriosclerosis, hypertrophied heart, aortic and mitral regurgitation. Blood pressure, 215 mm. Hg. Urine gave a large precipitate with acetic acid and potassium ferrocyanide, but none by heat.

"September 15: Urine contained a large amount of albumose, but no serum albumin.

"October 17: Urine showed precipitate with acetic acid and potassium ferrocyanide, but none on boiling.

"December 2: An attack of acute paroxysmal pulmonary edema. Very cyanotic. Frothy, serous expectoration. These attacks have been noted several times in the last four years, occurring at night and lasting several hours.

"December 10: Urine showed (1) an opacity at 50° C., precipitate at 70° C., partial clearing on boiling; (2) complete precipitation with two volumes of saturated ammonium sulphate solution; (3) no precipitate in cold with acetic acid.

"December 18: Examination of chest shows small elevations on ribs almost nodular, but no tenderness. X-ray picture of chest does not show any bony changes.

"December 23: Differential leukocyte count normal. Hemoglobin, 58 per cent.

"January 7, 1912: Patient died suddenly after being out all day, apparently of acute dilatation. No autopsy was secured."

Specimen of urine submitted for our examination by Dr. Beck showed characteristic reaction for Bence-Jones protein; precipitation with heat and acetic acid between 54° C. and 60° C., partial clearing on boiling, reprecipitation on cooling. Filtrate yielded no test for protein. Typical reactions also were obtained with 25 per cent. nitric acid, and on addition of two volumes of saturated solution of ammonium sulphate. Urine: Clear; acid; specific gravity, 1013; no sugar; total protein, 1½ grams per liter (Tsuchiya); total chlorides, 5 grams per liter; no casts.

Case III.—S. S., white, male, aged sixty-four years. Patient of Dr. Henry M. Fitzhugh, Westminster, Md. Admitted to the Johns Hopkins Hospital, January 9, 1912, under the care of Prof. T. B. Futcher.

Complaint: Pain in the left lumbar region and at the navel. Family History: unimportant. Previous History: unimportant. Present Illness: began about two months ago, pain on left side under costal margin, worse in the afternoon and at night. Eructation, no vomiting, no blood in stools.

Examination: Large man, undernourished, slightly anemic. Pupils react normally. Thorax symmetrical. Lungs clear. Heart normal. Pulse normal, no marked peripheral sclerosis. Blood pressure, 180 mm. Hg. Abdomen: no abnormality other than palpable right kidney. Rather marked dermatographia. Exaggeration of deep reflexes. No general glandular enlargement. No enlargement or nodes noted over long bones or ribs. Tenderness over eleventh and twelfth ribs, on left side. Patient thinks he may have injured this side some six months ago.

Ewald test meal showed marked hyperacidity.

Blood: Red blood cells, 3,800,000; leukocytes, 14,000; hemoglobin, 55 per cent. Differential count shows increase in polymorphonuclear neutrophiles.

"*X*-rays: Lumbar spine negative. Ribs show small vacuolated areas; similar areas in right humerus, due to bone destruction. These areas are sharply defined and there is slight new bone formation around the edge, showing an attempt to limit the disease."

Urine gave characteristic precipitation at 54° C., complete at 60° C., partial clearing on boiling, reprecipitation on cooling. Filtrate free from protein. Precipitate insoluble in water, but readily soluble on heating with dilute sodium carbonate solution, latter removed by dialysis, leaving the protein in solution. With 25 per cent. nitric acid there was precipitation in cold with an almost clear solution on boiling, reprecipitation on cooling.

During twenty days of the patient's stay in the hospital the total daily amounts of urine were examined. The Bence-Jones protein was constantly present, and was the only protein demonstrable. The total amount of urine varied between 2000 and 2800 c.c. Specific gravity, 1006 to 1010; total protein, 5 to 7 grams (Tsuchiya); total chlorides varied from 1½ to 4½ grams; coarsely and finely granular casts were found at each examination.

Patient lived about thirteen weeks after leaving the hospital, all the urine being saved and sent to the laboratory, where examination showed the constant presence of the Bence-Jones protein and no other. He grew steadily feebler, with increasing pain, referred to the ribs on the left side. Toward the end there was a development of nodes along the ribs over the precordium, with falling in of the sternum and great pain on breathing and coughing. There was enlargement of the lymphatic glands in the right groin, with great pain in the distribution of the anterior crural nerve. Glossitis was also noted.

No autopsy was permitted.

Case IV.—E. B., white, female, aged thirty-seven years. Admitted to the Johns Hopkins Hospital April 22, 1912. Died May 9, 1912.

Complaint: rheumatism.

Family History: Father supposed to have died of cancer. Previous History: unimportant.

Present Illness: Began six months before admission with onset of sudden pain in the right hip, which increased so that she was obliged to stop work two weeks later. Walked with great difficulty. After two months a similar trouble appeared in the left hip. Coincident with the joint trouble she noticed increasing nervousness, numbness of hands, and awkwardness. Appetite poor, occasional vomiting unassociated with pain. Loss of 40 pounds in weight. Four weeks ago she noticed a painful lump in the right breast. Discovery of this lump was not elicited in taking the history, but during the physical examination.

Examination: Patient much emaciated. Slight general pigmentation, most marked in folds of the skin. Mild grade of ichthyosis simplex. Pupils react normally. Lungs clear. Heart normal. Hard, irregular mass in the right breast, with retraction of nipple and some puckering of the skin. Abdomen normal. Reflexes normal. No local or general glandular enlargement. Spine somewhat stiff. Some shortening of the right leg. Tender nodes on the sixth rib of the right side below the breast. Blood pressure, 140 mm. Hg.

Blood: Red blood cells, 4,000,000; leukocytes, 9200; hemoglobin, 74 per cent. Differential, normal. Wassermann, negative.

"*X*-ray examination shows carcinomatous metastases in head, ribs, both trochanters, both ilia, and right tibia. These metastases are slightly different from what one sees in simple ordinary metastases, in that the areas involved in the bones are sharply limited and do not seem to be invasive in character, as one ordinarily sees. The metastatic areas in the bone, at first glance, present the appearance more of a giant-cell sarcoma, as there is definite new-bone formation around the edge, showing an attempt had been made to limit the disease."

Urine: acid; clear; 1012 to 1018; no sugar; no casts; with heat and acetic acid there is a precipitation at 60° C., partial clearing on boiling, reprecipitation on cooling. Filtrate from this reaction gave no tests for protein. Total amounts of urine were studied for nine days, up to forty-eight hours before death. From the combined urines of this period the Bence-Jones protein was isolated by precipitation with two volumes of saturated ammonium sulphate and dialyzation until free from salt, the process being repeated three or four times until a clear, neutral, slightly amber colored fluid was obtained, which gave all the characteristic reactions for Bence-Jones protein in the pure state. This case will be reported in detail elsewhere.

The patient became rapidly weaker and semicomatose, with loss of control of sphincters, difficulty in swallowing, feeble, irregular heart, and death occured on May 9. No autopsy was secured, but a portion of the femur was removed for section.

"Section of bone and tumor showed epithelial cells of the glandular type in alveoli of different sizes and shapes, surrounded by a rather dense fibrous stroma. In this stroma there are two types of bone areas, old bone showing lacunar absorption by the cancer cells and typical islands of new-bone formation of the endosteal cell type. This was first described by von Recklinghausen as ostitis carcinomatosa."

III. General Consideration of the Urine. As has been so clearly demonstrated by Hopkins and Savory, the specificity of the reaction for Bence-Jones protein is dependent upon the relative stability of its compounds with neutral salts at the boiling temperature, and their instability at lower temperatures (45° C. to 60° C.). The saline concentration has a marked influence on the completeness of the reaction, following closely the laws defined by Hardy for globulins, but differing essentially in the temperature relation. Salts are similarly graded for Bence-Jones protein at 100° C. and for globulins at room temperature. It follows from the above consideration that in applying the heat and acid test to urine for the detection of protein it is important to heat slowly in order that the differences of temperature in the determination of precipitation may be apparent. Should coagulation begin well below the boiling point, more careful examination for the detection of unusual proteins (fibrinogen or Bence-Jones protein) are indicated. If this principle were impressed on students in their training, there is little doubt that many cases would be detected which are otherwise overlooked. In such instances of precipitation well below the boiling point, careful note should be made of any tendency toward clearing on boiling the specimen, and the test repeated with the aid of a water bath and a thermometer. Confirmatory tests are made by treating another specimen with a few drops of 25 per cent. nitric acid—when the initial turbidity in the cold is increased as we approach 60° C., and clears up more or less completely at 100° C., falling out again as the specimen cools. For further confirmation another specimen is treated with two volumes of saturated ammonium sulphate solution when a voluminous precipitation occurs, sometimes quite slowly. These tests are sufficient to establish the presence of Bence-Jones protein. Other tests for Bence-Jones body as it occurs in the urine and when isolated in the pure state may be found on reference to the table in Neuberg, *Der Harn*, 1911, i, 774. If serum albumin is also present it may be determined by first heating the acidified urine to 60° C. for one hour, cooling, filtering until perfectly clear, and boiling the filtrate.

At the outset of this investigation it was our intention to repeat the work of Magnus-Levy, Grutterink and de Graaf, and Abderhalden on the chemical constitution of the body isolated from our abundant material, but this field has been so satisfactorily covered by Hopkins and Savory as to render it unnecessary. A few notes may be made, however, on the relative advantages of the various methods of quantitative separation. For securing material without denaturing the protein, the salting with ammonium sulphate, dialyzing the precipitate, and repeating the process many times, probably yields the best result. This method has the objection that it is time-consuming, and does not free the protein from pigment.

It has been our experience that the urines containing this protein become dark on standing, even when preserved from putrefaction, and great difficulty was experienced in obtaining any precipitate which was not deeply pigmented. Various attempts were made to decolorize the urine before precipitating the protein by use of animal charcoal, Kieselguhr, or carbon black, but we could find no method which yielded a colorless filtrate which did not at the same time remove the greater part or all of the Bence-Jones body. Precipitates treated in thin dialyzing sacs of collodion with running water for weeks held tenaciously to the coloring matter. We also found, as has been noted by other observers, that the protein, when dried *in vacuo,* becomes dark, and these dried precipitates, in our experience, were never completely soluble in distilled water, which we consider an evidence of partial denaturization.

The alcohol precipitation would seem to be limited in its application to the treatment of small volumes, which may be rapidly handled, as the protein soon passes into an insoluble condition on prolonging its contact with the alcohol. Perhaps where facilities for refrigeration on a large scale are available the usefulness of this method may be extended.

For purposes of chemical analysis, where the denaturization, due to heating, is of no moment, we have devised a method which gives excellent results, especially in freeing the substance from pigment and leaving it as a fine dry powder.

The urine is filtered through paper, faintly acidulated with acetic acid, and placed in large bottles in the water-bath, which is kept at 60° C. over night. On removal from the bath, the greater part of the coagulum has settled to the bottom of the containers, which permits of decantation, or syphonage, of most of the supernatant urine. The precipitate is then repeatedly washed in the bottle by shaking with distilled water, and finally collected on a filter, and the washing continued until the filtrate is free from chlorine. The wet precipitate is then spread in Petri dishes in layers not more than 0.5 cm. thick, sealed, and placed in a freezing mixture of ice and ammonium chloride. The frozen material is rapidly transferred to a desiccator, packed in a freezing mixture. The desiccator is then quickly exhausted to a vacuum of 4 mm. or less, when the ice in the precipitate sublimes and is absorbed by the sulphuric acid, leaving the precipitate as a dry, crumbling mass, pale gray to white in color, which is easily pulverized. This material is insoluble in water, but readily dissolves in a dilute solution of sodium carbonate on heating, yielding a water-clear solution, from which the sodium carbonate can be easily removed by dialysis, leaving the protein in solution. Such a solution gives all the characteristic reactions for Bence-Jones protein in the pure state.

In Case I, the longest under observation, after the recognition of the proteinuria the amount excreted varied from 2 to 5 grams per liter, with an output of 2 or 3 liters in twenty-four hours. In Case III the amount reached as high as 7 grams per liter, with an output of urine about the same as in Case I. The smallest excretion was in Case IV, in which the maximum was 1.5 grams per liter and the average 0.25 to 0.5 gram.

In one of our cases (Case I) we have observed spontaneous precipitation of the protein on standing for several months. These specimens of urine were found on bacteriological tests to be sterile, and the initial alkalinity considerably increased, though the urines were not ammoniacal. This phenomenon has been previously noted by Bradshaw[7] and Rosenbloom,[8] and will be reported fully elsewhere.

Polyuria was present at some time during the course of the malady in all of our cases except one (Case IV).

A striking feature to which attention has not heretofore been called is the great diminution in chloride excretion. The daily output in Case I was 2 or 3 grams; Case II, 5 grams; Case III, 1.5 to 4.5 grams, and in Case IV, 1.2 to 1.4 grams. In one case (Case IV) careful functional tests were made by Drs. Fitz and Rowntree. These showed a phenolsulphonephthalein excretion of 23 per cent. for two hours; lactose, 8 per cent.; iodide present after seventy-two hours; total chlorides, 0.15 to 0.18 per cent. of the amount ingested. In this case, also, serum albumin was at times present, but no casts were found. In the other cases the Bence-Jones body was the only protein present. In Case III casts were constantly present. None were found in Cases I and II.

IV. Biological Reactions. Although the chemical side of the Bence-Jones protein has been fairly completely covered in recent years, the biological investigations have been meager and somewhat conflicting. Borchard and Lippmann[9] have reported the detection of the body in the blood and serum of fasting dogs fed with the substance. In an alkaptonuric patient, Gross and Allard[10] noted a marked increase of homogentisic acid after feeding with this protein, in contrast to results obtained on feeding similar amounts of casein. After injection intravenously and subcutaneously, various authors have reported the presence of specific precipitins in the serum or blood. Rostoski found the reaction did not differentiate the Bence-Jones body from other proteins of human origin. Hopkins and Savory concluded that it is less powerful as a precipitinogen than blood proteins, but that its solutions react slightly with antihuman serum. Massini[11] reported complement fixation with highly potent sera, and was able to differentiate between the blood proteins and the Bence-

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[7] Med. Chir. Soc., London, 1898, lxxxi, 259; British Med. Jour., 1898, i, 1136.

[8] Archives of Int. Med., 1912, ix, 255.

[9] Biochem. Zeit., 1910, xxv, 6.

[10] Zeit. f. klin. Med., 1907, xliv, 359.

[11] Deutsch. Archiv f. klin. Med., 1911, civ, 29.

Jones protein. Stokvis[12] noted the appearance of the protein in the urine of dogs after its injection intravenously or by the rectum. In our own experiments we have used the protein obtained by ammonium sulphate precipitation, and have been unable so far to secure a specifically active precipitin, finding only weak reactions of equal intensity for Bence-Jones and human blood serum, but are continuing the experiments with larger doses and with the substance in various states. In all our rabbits, injected intravenously for the production of precipitins, there was commonly anuria for twenty-four hours, followed, in some instances, by the excretion of the protein in the urine in the next forty-eight hours, while after the second injection none of the animals excreted the protein as such.

Intradermal skin tests for sensitization were made, with the same lot of material used for other biological tests, with negative results. The test was applied to a considerable number of individuals, normal persons, and others with various pathological conditions, 4 of whom had bone metastases from carcinoma and sarcoma, inclusive of Case IV. Instillation of the solution into the conjunctiva of Case I did not produce a reaction, nor was any obtained in a case of multiple sarcomatous metastases to the bones. Anaphylactic tests on guinea-pigs are in progress, and other biological investigations with this protein have been undertaken.

V. SUMMARY. From the fact that the writers have observed 4 cases in fifteen months, it would seem that this type of proteinuria is probably more common than the literature would lead one to suppose.

Of these cases, 2 (Case I and Case III) were clinically multiple myeloma, and a third (Case II) was probably of the same type, although we have no objective proof. The remaining case (Case IV) was one of metastatic carcinoma from the breast, and is, we think, unique, as the case reported by Oerum[13] was associated with metastases from a gastric carcinoma. This case will be reported in detail elsewhere. It is especially interesting to note that the detection of the last three followed definitely the interest aroused among local physicians by the presence of the first case, which led them to test the urine of their patients more carefully. We should like to emphasize the fact that the recognition of the Bence-Jones body in the urine in each instance antedated any suspicion of the true nature of the malady, with the exception of Case IV, which was clearly associated with carcinomatous metastases. That this type of proteinuria may be present for some time before any clinical evidence of myelomatosis appears is shown by the first 3 cases noted.

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[12] Nederl. Tidj. v. Geneesk, 1891, ii, 136; Maly's Jahr d. Thier. Chem., 1891, xxi, 412.

[13] Ugesk. f. Laeger., 1904, 5 s., xi, 559; Abst. Biochem. Zentrlbl., 1904-5, iii, 203.

In Cases I and III the palpable bone tumors developed only late in their course. In Case II death occurred from an intercurrent disease before the appearance of any symptoms suggesting bone involvement, and the skiagrams taken twenty days before death showed normal bone shadows. In Case I the *x*-ray pictures, as above noted, were imperfect, but showed a laminated rarefaction of the tibia. In Case III the radiologist made a diagnosis of an unfamiliar type of vacuolization in the bones prior to the appearance of any palpable bone tumors, while in Case IV an accurate diagnosis of metastatic carcinoma of the bones was made.

The blood picture in our cases showed nothing abnormal except a secondary anemia. All the patients were aged over fifty years, except the case of carcinomatosis (Case IV). In all there was evidence of great metabolic disturbance in the extreme emaciation. Spontaneous fracture of ribs occurred in 2 cases. The development of metastatic nodes in the soft tissues, as in Cases I and III, is unusual in myelomatosis. Both of these had also glossitis.

In connection with Case I, it is noteworthy that there was marked hypertrichosis, macroglossia, keratosis of the palms, and soles, and scleroderma. These point to some disturbance of the internal secretions which may have been coincidental. Fitz[14] has reported, however, Bence-Jones proteinuria in myxedema.

In regard to possible changes in the kidney, we can say nothing from the morphological standpoint, as we had no autopsies, but would merely call attention to the striking fact that the kidney was permeable for the Bence-Jones protein, but held back serum albumin (except just before death in Case IV), and in all cases there was a striking diminution in the chloride excretion. These would seem to indicate functional disturbance of the kidney rather than a true nephritis.

In closing we take opportunity to express our thanks to Drs. Wilson, Beck, Fitzhugh, and Futcher for access to their cases, and to Profs. Barker and Halsted for use of material in their services. Special thanks are due Dr. Baetjer for his interest in the radiographic studies, and to Drs. Fitz and Rowntree for the functional tests.

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[14] Amer. Jour. Med. Sci., 1898, cxvi, 30.